

Routes to Expedite Vaccine Approvals

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The Need for Expedited Pathways

- Emerging and re-emerging diseases (*e.g.*, SARS)
- Pandemic strains of influenza
- Vaccine shortages (*e.g.*, PCV-7, influenza)
- New vaccines of local and global public health importance (*e.g.*, TB, malaria, HIV, HPV, rotavirus)
 - Orphan Vaccines in the U.S.
- Bio-terrorism agents (*e.g.*, smallpox, anthrax, plague)

Vaccine Licensure

- The development of a vaccine is a complex process resulting in the licensure and commercialization of a product that has been *demonstrated to be safe and effective* and that *can be manufactured in a consistent manner*.
- The FDA is committed to fostering the efficient, rapid development of vaccines needed for the public health.

Expediting the Review Process: Formal Mechanisms

- Fast Track
- Priority Review
- Accelerated Approval
- Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review (September, 1998)
 - <http://www.fda.gov/cber/guidelines.htm>

Fast Track Drug Development

- Designed to facilitate the development and expedite the review of new drugs that are intended to treat *serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs.*
- Intended to meet the need of Section 112(b) of the Food and Drug Administration Modernization Act of 1997.

Fast Track

- Incorporates an end of Phase I meeting
- Allows for a priority review of the BLA; allows for a “rolling” review of the BLA
- Allows for an accelerated approval of the product

Accelerated Approval

- Approval based on a determination that the effect of a surrogate endpoint is *reasonably likely* to predict clinical benefit (21 CFR 314.510 & 601.41)
- Post-licensure studies required
- There may be problems obtaining subsequent controlled clinical data

Priority Review

- 6 Month review of the entire BLA
- The review clock will not begin until the applicant has informed FDA that a complete BLA has been submitted
- Allows for a “rolling” review, i.e., review by segments of the application (CMC, statistical, clinical, etc)
- The pneumococcal conjugate vaccine, Prevnar, is an example of a vaccine that was given a priority review.

The "Animal Rule": an Innovative Approach to Regulation

- *New Drug and Biological Drug Products: Evidence Needed to Demonstrate Effectiveness of New Drugs when Human Efficacy Studies are not Ethical or Practical.*
 - Federal Register 67:37988-37998 May 31, 2002
 - 21 CFR 601.90-95 (biologicals)
 - 21 CFR 314.600-650 (drugs)
- For new drug and biological products that are intended to treat or prevent life-threatening or serious conditions.
- Use of animal efficacy data for approval

The “Animal Rule”

This rule will apply when adequate and well-controlled clinical studies in humans cannot be ethically conducted because the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers and field trials are not feasible prior to approval.

The “Animal Rule” (cont’d)

This rule will apply when there is a reasonably well-understood pathophysiological mechanism for the toxicity of the chemical, biological, radiological, or nuclear substance and its amelioration or prevention by the product.

The “Animal Rule” (cont’d)

This rule will apply when the effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans.

The “Animal Rule” (cont’d)

This rule will apply when the data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information in animals and humans is sufficiently well understood to allow selection of an effective dose in humans, and it is therefore reasonable to expect the effectiveness of the product in animals to be a reliable indicator of its effectiveness in humans.

The “Animal Rule” (cont’d)

- Will not apply if approval can be based on standards described elsewhere (surrogate markers or clinical endpoints other than survival or irreversible morbidity).
- Safety evaluation of products is not addressed by this rule (*i.e.*, human safety studies needed).
- Approval subject to post-marketing studies

Project BioShield Act of 2004

- Provides for research and development of countermeasures against various agents that may be used in a terrorist attack
- Provides for creation of a national stockpile of drugs, vaccines, and other biological products, medical devices, and other supplies “to provide for the emergency health security of the United States ...” The vendor shall seek approval, clearance, or licensing

Project BioShield Act of 2004

- Provides for Emergency Use Authorization
 - Emergency declared by Secretary of Homeland Defense or Secretary of Defense
 - EUA granted by Secretary of HHS
- Products known and potential benefits must outweigh the known and potential risks.

Project BioShield Act of 2004

- The product's use and distribution can be limited
- The authorization will be time-limited to one year but can be terminated earlier; the authorization can be renewed

Pandemic Influenza

- Use existing mechanisms for current licensed influenza vaccines
- Carry out studies with a strain to which the population is naïve (*e.g.*, H5N1)
- Pre-determine dosage and schedule
 - One dose or more needed
 - 15 µg or more or less
 - The potential for adjuvants

Orphan Drugs and Exclusivity

- United States Orphan Drug Act (PL-97-414) of 1983; *see also*, 21 CFR 316.3
- For Drugs and Biologics intended to treat 200,000 persons or fewer in the United States
- Orphan Drug designation can be granted at any stage in the drug development cycle
- Orphan Drug designation is public

Orphan Drugs and Exclusivity

- Tax credit equal to 50% of eligible clinical investigation expenses
- Seven year marketing exclusivity; may be more than a single orphan drug for the same indication (*e.g.*, if the second orphan drug is clinically superior to the innovator's drug)
- Sponsor may be able to compete for Orphan Drug Product Grants, administered by FDA's Orphan Drug Product Office (Dr. Debra Lewis; telephone 301-827-3666)

Speeding Product Development

- Early and frequent consultation between sponsor and FDA (improves quality and efficiency/reduces misunderstandings and potential for multiple cycles of review)
- Formal mechanisms
- Approval under the “animal” rule
- Emergency Use Authorization
- Attention to risk:benefit and risk management issues

The Fundamental Challenge

Regulations and the applications of regulations are dependent on the existing level of science that will support a particular action. The challenge for all of us is to identify the gaps in our knowledge, to identify the pathways – the Critical Path - to addressing those gaps, and to define the criteria for acceptability.

Dealing with uncertainty: taking risks

Nothing would be done at all if one waited until one could do it so well that no one would find fault with it.

- John Henry Cardinal Newman (1801 – 1890)